Increased Prevalence of Coronary Atery Aneurysms
Among Cocaine Users

Aaron Satran, MD; Bradley A. Bart, MD; Christopher R. Henry, BS; M. Bilal Murad, MD; Sumaiya Talukdar, BS; Daniel Satran, MD; Timothy D. Henry, MD

Background—Cocaine abuse has been implicated in multiple cardiovascular complications. Coronary artery aneurysms (CAAs) and ectasia occur in 0.2% to 5.3% of patients referred for angiography and are associated with atherosclerosis, Kawasaki’s disease, and several rare disorders. After observing CAAs in multiple young cocaine users, we investigated the prevalence of CAAs among cocaine users undergoing coronary angiography.

Methods and Results—Clinical and angiographic characteristics of 112 consecutive patients with a history of cocaine use and coronary angiography were compared with a control group of similar age and risk factors from an existing angiographic database over the same time period. Coronary angiograms were independently read by 3 reviewers blinded to cocaine use. Cocaine users were young (mean age, 44 years), predominantly male (80%), and cigarette smokers (95%). Control patients had higher rates of diabetes (33%) and more severe coronary artery disease ($P=0.01$). Previous myocardial infarction was common in both groups (45% of cocaine users, 38% of control patients). Despite the frequent history of myocardial infarction among cocaine users, 48% had nonobstructive coronary artery disease. Among cocaine users, 34 of 112 (30.4%) had CAAs compared with 6 of 79 (7.6%) in the control group ($P<0.001$). Cocaine use was a strong predictor of CAA by univariate and multivariate analyses.

Conclusions—This is the first description of an association between cocaine use and CAA. The prevalence of CAA among cocaine users was higher than expected (30.4%), given such a young cohort. Cocaine use may predispose to the formation of CAA, which may in turn be a contributing factor to myocardial infarction. (Circulation. 2005;111:2424-2429.)

Key Words: cocaine ■ coronary aneurysm ■ dilatation, pathologic ■ myocardial infarction

In 2001, the National Institute on Drug Abuse estimated that 27.7 million Americans (12%) over 12 years of age had used cocaine at least once and that nearly 1.7 million had used it in the past month. Although cocaine use has declined since 1985, it remains the most commonly encountered illicit substance among those presenting to hospital emergency departments (30% of all drug-related visits). The cardiovascular effects of cocaine are well documented and include myocardial ischemia and myocardial infarction (MI), accelerated atherosclerosis, coronary artery vasoconstriction, dysrhythmias, cardiomyopathy, aortic dissection, malignant hypertension, in situ thrombus formation, and sudden cardiac death. In contrast, coronary artery aneurysms (CAAs), first described by Morgagni in 1761, are infrequent. CAAs, defined as aneurysmal dilatations $>1.5$ times the normal coronary segment, can be divided into discrete aneurysms (localized dilatation, either saccular or fusiform) or ectasia (diffuse dilatation involving $>50\%$ of the artery). The incidence of CAA ranges from 0.2\% to 5.3\%, with the largest antemortem series found in the Coronary Artery Surgery Study (CASS) registry (4.9\% of 20 087 patients referred for coronary angiography). CAAs are most commonly associated with atherosclerosis but also are reported with Kawasaki’s disease, arteritis (polyarteritis nodosa, syphilis, systemic lupus erythematosis, Takayasu’s arteritis), mycoses, trauma, connective tissue disorders (Marfan’s and Ehlers-Danlos syndromes), metastatic tumors, polycystic kidney disease, and percutaneous coronary interventions. An association between CAA and cocaine use has not been reported. After observing the presence of severe coronary ectasia in several young cocaine users, we hypothesized that cocaine use increases the prevalence of CAA.

Methods
This study was approved by the Human Subjects Research Committee at Hennepin County Medical Center. The study population included 112 consecutive patients over a 10-year period with a history of cocaine use and coronary angiography as identified by billing codes. Charts were reviewed for age, sex, race, cardiac risk factors, indications for coronary angiography, and cardiac events, including previous MI, CABG, or percutaneous coronary intervention. To provide a control group, a cohort of similar age and risk factors (CASS) registry (4.9\% of 20 087 patients referred for coronary angiography). CAAs are most commonly associated with atherosclerosis but also are reported with Kawasaki’s disease, arteritis (polyarteritis nodosa, syphilis, systemic lupus erythematosis, Takayasu’s arteritis), mycoses, trauma, connective tissue disorders (Marfan’s and Ehlers-Danlos syndromes), metastatic tumors, polycystic kidney disease, and percutaneous coronary interventions. An association between CAA and cocaine use has not been reported. After observing the presence of severe coronary ectasia in several young cocaine users, we hypothesized that cocaine use increases the prevalence of CAA.
factors was selected from a preexisting angiographic database of 300 consecutive patients within the time period of the study group. To provide a similar age distribution, all patients 52 years of age were included, with cocaine use the only exclusionary criterion.

Using criteria previously described in the literature,8–14 3 independent readers (T.D.H., B.A.B., M.B.M.) evaluated angiograms of both the study and control patients for CAA for the presence of coronary artery disease (CAD; none, nonobstructive [≤50% stenosis], or 1-, 2-, or 3-vessel disease). Definite aneurysmal disease was defined as agreement by all 3 readers as to the presence of CAA (n=24); probable CAA was classified as agreement among 2 of the 3 readers (n=10). If only 1 reader reported aneurysmal disease, that particular patient was classified as having possible CAA but was not included in the final analysis (n=8). The readers were blinded to clinical characteristics of the patients, including the presence of cocaine use, and both the control and study groups were analyzed in a similar fashion.

Statistical Analysis

Clinical characteristics of the 2 groups were compared by use of Pearson’s χ² analysis and Fisher’s exact test (when appropriate) for dichotomous variables. Student’s t test was used for continuous variables.

Univariate predictors of CAA were determined by logistic regression, χ² test, or Fisher’s exact test. Multivariate predictors of CAA were determined through the use of a stepwise logistic regression, with 0.2 and 0.05 as the significance levels for entering and removing variables, respectively. The stepwise logistic regression was performed forcing age and gender into the model. Statistical analyses were performed with SAS version 8.02 software (SAS Institute Inc).

Results

Clinical Results

The clinical characteristics of all patients are presented in Table 1. The 112 patients with a history of cocaine use were young (mean age, 43.7±8.1 years) and predominantly male (79%). Cocaine users were nearly all cigarette smokers (95%) and commonly hypertensive (73%) and hyperlipidemic (71%); diabetes (16%) was less common. The 79 patients in the control group were also young (mean age, 45.6±4.9), although a smaller percentage were male (61%). Although the control group was similar in nearly all clinical characteristics, there was a higher rate of diabetes (P=0.01) and severity of CAD (P=0.01). Compared with the control group, cocaine users were more likely to be cigarette smokers and to have normal coronary arteries.

Of the patients with reliable documentation regarding frequency and method of cocaine abuse, 66% reported at least weekly use. Sixty-nine percent reported smoking or intranasal use; 7%, intravenous use; and 24%, multiple routes of administration.

TABLE 1. Clinical and Angiographic Characteristics

<table>
<thead>
<tr>
<th>Clinical, n</th>
<th>Cocaine</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>43.7±8.1</td>
<td>45.6±4.9</td>
<td>NS</td>
</tr>
<tr>
<td>M/F, n (%)</td>
<td>89/112 (79)</td>
<td>48/79 (61)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetes mellitus (types I and II), n (%)</td>
<td>16/102 (16)</td>
<td>26/79 (33)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>77/105 (73)</td>
<td>48/78 (62)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (current and former), n (%)</td>
<td>98/103 (95)</td>
<td>55/78 (71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous MI*, n (%)</td>
<td>49/110 (45)</td>
<td>31/79 (39)</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular hypertrophy,† n (%)</td>
<td>49/94 (52)</td>
<td>23/34 (68)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia,‡ n (%)</td>
<td>48/68 (71)</td>
<td>53/68 (78)</td>
<td>NS</td>
</tr>
<tr>
<td>Indications for catheterization, n (%)</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>38/112 (34)</td>
<td>37/79 (47)</td>
<td></td>
</tr>
<tr>
<td>Stable angina/positive ETT</td>
<td>22/112 (20)</td>
<td>27/79 (34)</td>
<td></td>
</tr>
<tr>
<td>CHF/cardiomyopathy</td>
<td>30/112 (27)</td>
<td>4/79 (5)</td>
<td></td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>18/112 (16)</td>
<td>7/79 (9)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmias/valvular disease</td>
<td>4/112 (4)</td>
<td>4/79 (5)</td>
<td></td>
</tr>
<tr>
<td>CAD classification, n (%)</td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>39/112 (35)</td>
<td>13/79 (16)</td>
<td></td>
</tr>
<tr>
<td>Mild (&lt;50% stenosis)</td>
<td>14/112 (13)</td>
<td>12/79 (15)</td>
<td></td>
</tr>
<tr>
<td>1-Vessel disease</td>
<td>24/112 (21)</td>
<td>14/79 (18)</td>
<td></td>
</tr>
<tr>
<td>2-Vessel disease</td>
<td>23/112 (21)</td>
<td>19/79 (24)</td>
<td></td>
</tr>
<tr>
<td>3-Vessel disease</td>
<td>12/112 (11)</td>
<td>21/79 (27)</td>
<td></td>
</tr>
</tbody>
</table>

ETT indicates exercise tolerance test; CHF, congestive heart failure.
*History of ischemic chest pain or equivalent with concurrent elevation in cardiac enzymes.
†As defined by standard echocardiographic and ECG criteria.
‡Total cholesterol ≥200 mg/dL.
stable angina/positive stress test, 5% congestive heart failure/ cardiomyopathy, 9% atypical chest pain, and 5% arrhythmias/valvular disease. Therefore, 81% of the control group were referred for coronary angiography because of CAD in contrast to 54% of the cocaine users, who were more often referred for evaluation of congestive heart failure/cardiomyopathy (Table 1) \( P < 0.001 \).

### Angiographic Results

Approximately half of the cocaine users (48%) had angiographically normal coronary arteries or nonobstructive CAD, 21% had 1-vessel disease, 21% had 2-vessel disease, and 11% had 3-vessel disease (Table 2). CAD was more frequent in the control group: 18% had 1-vessel disease, 24% had 2-vessel disease, and 27% had 3-vessel disease. Thirty percent of the patients in the study group (34 of 112) had CAA, either definite \( n = 24 \) or probable \( n = 10 \) (Table 2 and Figures 1 through 4). An additional 8 patients had possible CAA. Among patients with CAA, 8 of 34 (24%) had angiographically normal or nonobstructive CAD. Among patients with a history of MI, 7 of 49 (14%) had angiographically normal or nonobstructive CAD. In contrast, only 6 of 79 (7.6%) control patients had CAA, including a patient with vasculitis and 2 patients with end-stage renal disease.

### Predictors of CAA

A univariate analysis was performed on the cocaine users and the entire study population to evaluate predictors of CAA (Table 3). Among cocaine users, previous MI and the presence of CAD were statistically significant predictors of CAA. For the entire population, previous MI and cocaine use were the strongest predictors of CAA, whereas the presence of CAD, hypertension, and smoking were also predictive.

A multivariate analysis was performed on the entire study population using a stepwise regression with an entry significance level of 0.2. Smoking was excluded from the model because of its collinearity with cocaine use. Only cocaine use (odds ratio, 8.06; 95% CI, 1.74 to 37.45; \( P < 0.008 \)) and previous MI (odds ratio, 3.55; 95% CI, 1.30 to 9.68; \( P < 0.013 \)) remained significant independent predictors of CAA.

### Discussion

Cocaine blocks the presynaptic reuptake of epinephrine, norepinephrine, serotonin, and dopamine, thereby enhancing sympathomimetic activity and affecting the cardiovascular system via multiple mechanisms. With small doses of intranasal cocaine hydrochloride (a topical anesthetic), Lange et al.\(^\text{24}\) demonstrated increased heart rate and systemic arterial pressure and decreases in coronary sinus blood flow and left coronary arterial diameters. Accelerated atherosclerosis resulting from cocaine use is strongly suggested by autopsies of young cocaine users showing an increased frequency of significant CAD.\(^\text{25–28}\) Cocaine-related myocardial ischemia and MI have been well documented, both in patients with angiographically normal coronary arteries\(^\text{29}\) and in more with underlying atherosclerosis.\(^\text{30–33}\) A study by Mittleman et al.\(^\text{33}\) was the first to demonstrate a large, abrupt, and transient increase in the risk of acute MI in cocaine users. Cocaine has been shown to enhance platelet aggregation\(^\text{34,35}\) and thrombosis\(^\text{32,36–39}\) and to promote transient erythrocytosis.\(^\text{40}\) Additionally, the vasoconstrictive effects of cocaine are seen in both dysfunctional\(^\text{41}\) and histologically normal endothelial.\(^\text{42}\) In summary, the pathophysiology of cocaine-related
myocardial ischemia and MI can be due to 1 or any combination of the following: increased oxygen demand in the setting of a fixed supply, coronary artery vasoconstriction, and a procoagulant state.6

Most (≈50%) CAAs are thought to be atherosclerotic in origin on the basis of microscopic findings of hyalinization and lipid deposition, destruction of the intima and media, focal calcification and fibrosis, and foreign body giant cell reaction.17,18 Inherent in this theory is the concept of an abnormal vessel media that may be predisposed to aneurysm formation via plaque degeneration or chronic overstimulation by various agents, including nitric oxide.43 Studies have shown that even nonatherosclerotic forms of CAA have in common extensive medial degeneration with functional loss of elasticity and replacement of smooth muscle by hyalinized collagen.19,44 These structural changes might imply that ectatic coronary arteries have minimal vasoreactivity, but case reports suggest that coronary ectasia, even in the absence of obstructive disease, can result in angina, vasospasm,45 myocardial ischemia, and MI.46 Krüger et al47 demonstrated exercise-induced myocardial ischemia and inappropriate coronary vasoconstriction in patients with nonatherosclerotic CAA who were given intracoronary nitroglycerin, providing further evidence for medial and endothelial dysfunction associated with CAA.

This is the first reported association between CAA and cocaine use. Potential mechanisms for the development of CAA related to cocaine include severe episodic hypertension and vasoconstriction with direct endothelial damage predisposing to aneurysm formation. It is possible the aneurysmal disease may be related to underlying atherosclerosis, given the concurrent risk factors such as cigarette smoking, hypertension, and hyperlipidemia. Nonetheless, the extremely high prevalence of CAA in cocaine users is striking compared with the control group and previous series of patients with CAD. Furthermore, the presence of CAD was not an independent predictor of CAA in the multivariate analysis. Finally, the members of the control group had more atherosclerosis and were more likely to undergo coronary angiography on the basis of CAD, yet CAAs were much less common. Cocaine use should be considered a risk factor for CAA, in addition to its other cardiovascular effects.

Limitations of our study include a lack of reliable documentation regarding the frequency and duration of cocaine abuse and route of administration for all patients. In addition, our study only includes patients referred for angiography.
Although the total number of patients with cocaine-associated chest pain admitted to the hospital or evaluated in the emergency department was higher, it was difficult to obtain accurate information for the same time period.

The natural history of CAA is uncertain, given its relatively uncommon occurrence and lack of longitudinal data. Intracoronary thrombosis does occur in patients with CAA, but the incidence has not been previously reported. Our data also support an association between CAA and acute MI. Nearly half the patients (49 of 112) in the cocaine group had a history of acute MI despite an average age of 43 years, >10 years younger than cohorts in previous studies of CAA. Seven infarctions occurred in patients with nonobstructive CAD, suggesting that CAA or enhanced vasoreactivity may be a predisposing factor to cardiac events in this population. These findings are consistent with a previous study by Demopoulos et al in which a history of acute MI was reported among 39% of patients with CAA and no CAD. Of 34 patients with CAA, 22 had previously sustained an acute MI. The availability of more potent, well-tolerated antiplatelet therapy provides potential treatment strategies that deserve further investigation in this group of patients. Aneurysmal rupture is another theoretical concern, although it has never been documented premortem and appears to be extremely rare.

**Conclusions**

Patients with a history of cocaine abuse have an increased prevalence of CAA. These patients appear to be at increased risk of acute MI, providing another potential mechanism of acute MI in cocaine users.

**Acknowledgment**

We are indebted to Marilyn Chazin-Caldie for her assistance in the statistical analysis.

**References**


### Table 3. Univariate Analysis: Clinical Parameters for the Presence of CAA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cocaine Users (n=112)</th>
<th>All Patients (n=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95% CI P</td>
<td>RR 95% CI P</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.11 0.92–1.33 0.31</td>
<td>1.15 0.95–1.39 0.19</td>
</tr>
<tr>
<td>HTN</td>
<td>1.70 0.70–4.16 0.25</td>
<td>0.89 0.45–1.75 0.72</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.25 1.01–1.54 0.07</td>
<td>1.27 1.05–1.54 0.04</td>
</tr>
<tr>
<td>AMI</td>
<td>1.08 1.01–1.15 0.12</td>
<td>1.16 1.04–1.29 0.04</td>
</tr>
<tr>
<td>LVH</td>
<td>1.75 1.18–2.59 &lt;0.01</td>
<td>1.75 1.28–2.40 &lt;0.01</td>
</tr>
<tr>
<td>CAD</td>
<td>1.40 0.96–2.04 0.09</td>
<td>1.28 0.94–1.74 0.15</td>
</tr>
<tr>
<td>Cocaine Use</td>
<td>1.81 1.31–2.49 &lt;0.001</td>
<td>1.30 1.03–1.65 0.05</td>
</tr>
</tbody>
</table>

HTN indicates hypertension; AMI, acute MI; and LVH, left ventricular hypertrophy.


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